REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the remarks which follow.

As noted in the Office Action Summary, claims 16-34 are currently pending. Claims 16, 25, 27, and 30 are amended herein. Claims 32 and 33 are cancelled as redundant in light of amendments made herein. Basis for these amendments may be found throughout the specification and claims as-filed, especially at page 5, line 25 to page 6, line 6 (regarding hydrophilic components), page 6, line 26 to page 7, line 2 (regarding tablet lacquering, *i.e.*, coating, with a HPMC and HPC suspension), page 1, lines 3-7 and page 7, lines 9 and 10-14 (regarding the controlled release properties of the formulation). Thus, no prohibited new matter is presented herein. Applicants reserve the right to file at least one continuation or divisional application directed to any subject matter canceled by way of the present Amendment.

Rejections Under 35 U.S.C. § 112

Claims 16-34 stand rejected under 35 U.S.C. § 112, second paragraph, as purportedly indefinite.

The Office states that the phrase "wherein the hydrophilic component comprises about 15-18 weight percent of the formulation", as recited by the independent claims (*i.e.*, claims 16 and 27), is indefinite. Specifically, the Office asserts that the term "hydrophilic component" is a broad term and so it is purportedly unclear as to what is included in this term.

In response, Applicants first refer to page 5, line 24 to page 6, lines 6 which discuss what is meant by the term "hydrophilic component". Specifically, the

specification discloses the required characteristics of the hydrophilic component for use in the presently claimed invention, including the ability to increase the viscosity of the microenvironment, and the ability to stabilize the viscous layer. The skilled artisan, based on what is known in the art, would not include lactose as having these properties, and thus the skilled artisan would not include lactose as a hydrophilic component in the claimed invention.

However, in the interest of expediting prosecution, and without acquiescing in the rejection, independent claims 16 and 27 are amended herein to recite that the hydrophilic component is alkyl-substituted cellulose ethers, polysaccharides, adsorbants, or mixtures thereof, as suggested by the Examiner. These hydrophilic components are supported by the specification, at least on page 5, line 25 to page 6, line 6.

Claim 32 stands rejected as reciting "fatty alcohol" as a hydrophilic component. Claim 32 is canceled herein as redundant, in light of the amendment to base claim 27. Thus, this rejection is moot.

Claim 32 stands rejected as reciting "large specific surface adsorbants". Claim 32 is canceled herein as redundant, in light of the amendment to base claim 27. Thus, this rejection is moot.

Claim 25 stands rejected as reciting "characterized in that the tablet is lacquered". The Office states that a tablet cannot be lacquered, although a lacquered finish may be applied to a tablet. In order to further clarify the present invention, claim 25 is amended herein to replace "lacquered" with "coated", in order to show that the term lacquered referred to the coating of the tablet and not the tablet itself.

In light of the above remarks and amendments to the claims, Applicants request that the rejections under 35 U.S.C. § 112, second paragraph be withdrawn.

Rejections Under 35 U.S.C. § 102

Claims 16, 24, 29-30 and 32-33 stand rejected under 35 U.S.C. § 102 as purportedly anticipated by Yajima et al. (U.S. Patent No. 5,707,646; "Yajima").

Applicants submit that Yajima fails to recite every element of the presently claimed invention, especially as amended herein. To anticipate a claim, a single prior art reference must teach each and every element of the claimed invention. *See* M.P.E.P. § 2131; *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987); *Hybritech Inc.v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986).

First, independent claims 16 and 27 are amended herein to clarify that the claimed formulation has controlled release properties, as noted throughout the specification as-filed. Claim 29 recites controlled release properties as well. Yajima does not disclose or even suggest any controlled release properties of its formulation. Rather, Yajima only discloses that the formulation has taste masking properties. Taste masking is quite different from controlled release, and is actually much easier to achieve with a formulation designed to be taken perorally, than the controlled release property of Applicant's formulation.

The controlled release aspect of Applicants' formulation requires that the release profile of any single active ingredient must be carefully adjusted to achieve a precise amount of the timely delivered active ingredient, in order to maintain a therapeutically sufficient blood level of the active ingredient throughout the day.

Thus, a controlled release formulation, and the preparation of a controlled release formulation, is very different from the normal, instant or immediate release dosage of Yajima, where no adjustment is required.

The Office asserts that as the present claims are directed to any hydrophilic component, then the fatty components disclosed by Yajima are included in the presently claimed invention. Independent claims 16 and 27 are amended herein to recite hydrophilic components which do not include the stearyl alcohol and maltitol disclosed in Yajima. Thus, the present claims are structurally distinguishable from what is disclosed in Yajima.

Finally, The Office also cites to Example 6 of Yajima, which discloses 10% of clarithromycin. Applicants note that this amount of clarithromycin, when applied to Applicants' formulation, would require an extremely high dosage (500 mg) of clarithromycin. A tablet containing this amount of clarithromycin, as made by Applicants' formulation, would weight at least 5,000 mg, and so would be much to big for a patient to swallow.

Claims 16, 19, 24, and 27-33 stand rejected under 35 U.S.C. § 102 as purportedly anticipated by Briskin et al. (WO 95/223109; "Briskin"). Briskin fails to recite each element of the present invention as claimed herein, and thus Applicants traverse.

Applicants claimed invention is directed to a peroral, daily controlled release lipid-hydrophilic matrix, which allows for control of the release of the active substance throughout the day. Other components such as surface tension modulators or pH modulators may be added.

Briskin, in contrast, does not disclose a controlled release formulation or even a single daily formulation. Instead, Briskin discloses the ability to prepare an extrusion of the formulation mass without destruction of equipment. In fact, Briskin does not disclose any precise composition of the formulation, as required with a controlled release formulation, and even fails to disclose the final form of the formulation.

Finally, the present invention and Briskin disclose different processes, as well as different effects of the formulations. Briskin even discloses different uses of the active ingredient. In Briskin, clarithromycin is combined with some excipients whose function is not described, with the exception of glyceryl behenate, which is used only as an extrusion aid.

In light of the above comments and amendments to the claims, Applicants submit that Briskin each fails to recite each element of the present claims, and request that the rejections under 35 U.S.C. § 102 be withdrawn.

Rejections Under 35 U.S.C. 103

Claims 17-18, 20-21, 23, and 25-28 stand rejected under 35 U.S.C. § 103 as purportedly unpatentable over Yajima et al. Applicants respectfully traverse.

For a *prima facie* case of obviousness, the following three requirements must be met. First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference or to combine the reference with another reference. Second, the proposed modification must have had a reasonable expectation of success, determined from the vantage

point of the skilled artisan at the time the invention was made. Third, the prior art reference must teach or suggest all the limitations of the claims. The teachings or suggestions as well as the expectation of success must come from the prior art and not from applicant's disclosure. *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988); *Amgen, Inc. v. Chugai Pharm. Co.,* 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991); and *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Applicant respectfully submits that these criteria have not been met in the present Office Action.

First, as discussed above, Yajima fails to disclose each element as claimed in the present invention. Claim 16 (upon which claims 17-18, 20-21 and 23 depend) is amended herein to recite that the claimed formulation is a controlled release formulation, as well as to recite specific hydrophilic components not recited in Yajima. Thus, Yajima does not recite each element of the present invention.

Further, Yajima fails to provide motivation to arrive at the present invention or an expectation of success. Controlled release formulations are very different in preparation, composition, and effect, from non-controlled release formulations. Controlled release formulations require that the release profile of any singular active ingredient be carefully adjusted to achieve a precise amount of the *timely delivered* active ingredient. This step is extremely important in order to maintain a therapeutically sufficient blood level of the active ingredient throughout the day. Yajima provides no discussion of a controlled release property or any motivation to attempt it. The skilled artisan would certainly not attempt it on their own, due to the specific and painstaking adjustments required, especially as Yajima does not disclose any disadvantage to its own non-controlled release formulation.

In addition, Yajima discloses a formulation of 10% clarithromycin. This amount of clarithromycin, when applied to Applicants' formulation would require an extremely high dosage (500 mg) of clarithromycin, requiring a tablet of at least 5,000 mg (*i.e.*, too big for a patient to swallow). In addition, such a high dosage of the active ingredient requires a very subtle design of the formulation, as there is not much of a difference between the mass of the active substance and the total mass of the composition. Each dosing would have to be designed separately to achieve a precisely desired release profile which has to match the reference product, in order to be bioequivalent. Thus, achieving a controlled release formulation using the percent amounts of ingredients of Yajima would be extremely difficult and improbable. Yajima certainly provides no motivation to attempt it.

Furthermore, Yajima discloses low substitution of HPMC. In contrast, the present invention is concerned with the viscosity of the HPMC, rather than the low or other preferred quantity of substitution of HPMC. As known by the skilled artisan, Applicants submit that there is no immediate correlation between the viscosity and substitution. This is because viscosity is driven by the cellulose chain length, whereas substitution may or may not be different for HPMCs having a different viscosity (for example, both Methocel E 50 P and E 15 LV have a very similar declared methoxy substitution of 29 and 28-30%, respectively, as well as a very similar hydroxypropyl substitution of 8.5 and 7-12%, respectively, but the corresponding viscosities are very different being 37.5-70 and 12-16 mPas, respectively). Further, a HPMC of a different viscosity has a different influence on the release profile. Thus HPMCs are definitely not interchangeable. Therefore, the

correlation made by the Office between Yajima and the present invention is not appropriate.

In light of the above comments, Applicants request that this rejection be withdrawn.

Claims 16-18 and 24-30 stand rejected under 35 U.S.C. § 103 as purportedly unpatentable over Ahlgren et al. (U.S. Patent No. 6,117,452; "Ahlgren"). Applicants traverse.

Applicants submit that Ahlgren fails to provide motivation to arrive at the present invention or an expectation of success or recite each element of the present invention. Specifically, the present invention is directed to a controlled release formulation or process of preparing same. Ahlgren fails to provide any motivation as to the formulations and processes of the present invention. Ahlgren is not directed to a controlled release formulation based on controlled release of the core, but rather to a "thermoformed composition" whereby release can be achieved only by the amount coating. In contrast, the controlled release properties of the presently claimed formulation is achieved already by the composition of the core. The coating of the claimed invention is not necessary to the controlled release, and would only potentially serve as a modifier.

Further, with regard to the active ingredient, Ahlgren provides a huge list, three columns long, of many possible types of active substances. There is no other teaching in the cited reference which would indicate that clarithromycin should be singled out from the provided list of hundreds of other active ingredients disclosed. As previously discussed, in order to achieve an effective controlled release, each

individual active ingredient must be considered on its own. Careful designing of each and every particular dose of each particular active substance is required. Thus, just disclosing a general "thermoformed composition", and providing a huge laundry list of active ingredients does not motivate the skilled artisan to the claimed invention or provide an expectation of success. Each active substance would have to be considered in a way completely different from the other listed active substances.

Finally, the Office notes PEG(32) glyceryl palmitostearate, as set forth on column 1, line 61 of Ahlgren, as a hydrophilic component. However, line 61 of column 1 of Ahlgren listed this composition as a fatty ester. In fact the term "hydrophilic" is not used in this reference. In any case, the claims are amended herein such that fatty esters are not listed as hydrophilic components.

Claim 22 stands rejected under 35 U.S.C. § 103 as purportedly unpatentable over Ahlgren in view of Gibson et al. (U.S. Patent No. 5,811,120; "Gibson"). Applicants traverse.

Gibson fails to remedy the deficiencies of Ahlgren, as detailed above. The Office cites "certain fatty acid combinations" as a hydrophilic component. As previously noted, the claims of the present invention are not directed to fatty acid combinations, and in fact, are amended herein recite components not including fatty acids.

Further, Gibson is clearly directed to raloxifene, which is a completely different substance than an antibiotic, including clarithromycin. The differences are both structural and with regard to handling properties. As known in the art of

pharmaceutical preparation, the release profile of a drug has to match the release profile of the originator reference (of the same drug). Therefore, Gibson fails to provide the skilled artisan with an expectation of success, as it is extremely unlikely that the profile required with the present invention would be the same as that of Gibson, especially with regard to the rigorous standards of the U.S. drug authorities. Even if the active ingredient of the present invention and that of Gibson had the same excipients, the skilled artisan could not create an analogous controlled release formulation simply by substituting substance. Even by changing the amount of one excipient in a ready controlled release formulation, the achieved release profile is expected to be ruined.

In summary, Gibson does not remedy the deficiencies of Ahlgren, as neither reference is directed to a controlled release formulation based on the core, especially with regard to clarithromycin. Thus, taken in combination, the cited references do not provide teaching, motivation or expectation of success to the skilled artisan with regard to making the Applicants' controlled release formulation.

Claims 17-18, 20-24, 26, and 34 stand rejected under 35 U.S.C. § 103 as purportedly unpatentable over Briskin in view of Gibson. Applicants traverse.

Gibson fails to remedy the deficiencies of Briskin. Briskin fails to recite each element of the present invention. As noted previously, Briskin fails to recite a controlled release formulation or even a single daily formulation. Nor does Briskin disclose a precise composition of the formulation as required with a controlled release formulation, and even fails to disclose the final form of the formulation

Combined together, Briskin and Gibson merely disclose overcoming problems not concerned with the present invention, such as extrusion without damaging the apparatus and equipment and the preparation of a direct compression oral formulation. Neither reference provides motivation to make the controlled release formulation of the present invention, let alone provide any expectation of success.

In light of the amendments to the claims and the above remarks, Applicants request that the rejections under 35 U.S.C. § 103 be withdrawn.

CONCLUSION

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of the application may be expedited.

Respectfully submitted,

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